Association Between Cardiovascular and Intraocular Pressure Changes in a 14-day 6º Head Down Tilt (HDT) Bed Rest Study: Possible Implications in Retinal Anatomy

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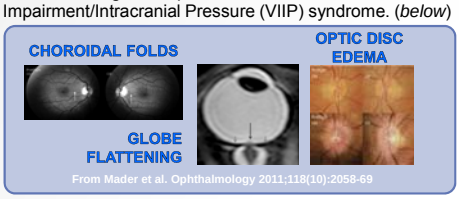
BACKGROUND

• History of visual impairment among astronauts with microgravity exposure.
• Numerous signs comprise the Visual Impairment/Intracranial Pressure (VIIP) syndrome. (*below*)



• Lack of data and analog studies have hindered development of preventive countermeasures.
• Current theory on VIIP etiology involves interaction of increased intraocular pressure (IOP), intracranial pressure (ICP), and genetic susceptibility.

PURPOSE

• Characterize HDT BR as possible VIIP syndrome model.
• Investigate association between ocular/cardiovascular parameters.

METHOD

• 14 day 6° HDT bed rest (+14 days pre-bed rest & +7 days post-bed rest).

• *Nomenclature:*

BR-13	-	BR-1	*Pre-bed rest phase*
BR1	-	BR14	*In-bed rest phase*
BR+0	-	BR+6	*Post-bed rest phase*

• 16 subjects: normotensive, non-smoker, normal weight/BMI
  • Male: 12
  • Female: 4
• Statistical modeling performed using mixed effects linear regression model with random intercepts for subject and eye (L/R) to account for the within subjects experimental design (software package: *Stata/IC 12.1*).

OCULAR MEASURES (BR-10, BR-3, BR3, BR10, BR+2)	
Intraocular Pressure (IOP)	Pre-/post-bed: *Goldmann* In-bed: *iCare (11 subjects), Tonopen (5 subjects)*
Retinal Nerve Fiber Layer (RNFL) Thickness	*Spectral-domain OCT*
Central Subfield Thickness	*Spectral-domain OCT*

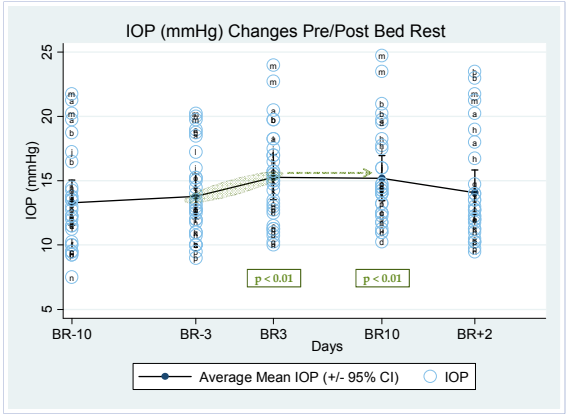
CARDIOVASCULAR MEASURES (BR-5, BR+0, BR+3)	
Blood Pressure (*Systolic, Diastolic*)	*Dinamap BP cuff*
Heart Rate	*Doppler ultrasound*
Stroke Volume	*M-mode echocardiography*
Plasma Volume	*Carbon monoxide rebreathing technique*
Cardiac Output	*CO = Stroke Volume x Heart Rate*

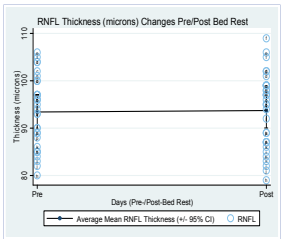
NASA Flight Analogs Research Unit (FARU) Standardized Conditions

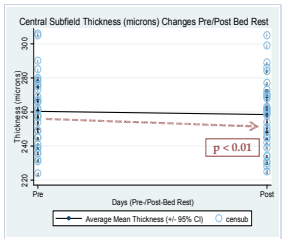
• During in-bed phase: subject reclined and monitored 24 hours/day
• Vitals, body weight, fluid intake/output measured daily
• Awake time: 6:00 am – 10:00 pm
• Standardized diet to maintain weight within 3% of initial weight

RESULTS

• Mean IOP at BR3 increased over baseline values from BR-3 ($p < 0.01$).
• Mean IOP at BR10 remained higher than baseline values from BR-3 ($p < 0.01$).
• Mean IOP approached baseline values by BR+2 and was no longer elevated at a statistically significant level ($p < 0.47$).
• Although mean IOP increased during the 6 HDT in-bed phase, it remained within the normal limits for subject safety.
• Analysis of RNFL Thickness with Cirrus HD-OCT showed no statistically significant changes ($p < 0.48$).
• Central subfield (macula) thickness decreased from an average of 260.31 µm at BR-10 to an average of 258.44 µm at BR+2 with statistical significance ($p < 0.01$).







	IOP					Average RNFL Thickness		Central Subfield Thickness	
Day	BR-10	BR-3	BR3	BR10	BR+2	Pre	Post	Pre	Post
Mean	13.30	13.78	15.28	15.20	14.09	93.41	93.72	260.31	258.44
CI +/- 95%	11.56/15.05	12.03/15.53	13.53/17.03	13.45/16.95	12.34/15.83	89.71/97.10	90.02/97.41	250.00/270.63	248.12/268.75
p (vs. BR-3)	0.25	-	<0.01	<0.01	0.47		0.48		<0.01

Fig. 1. IOP changes during pre-/in-/post-bed rest. Each circle represents IOP from either eye (left/right) and is labeled with a letter notating each different test subject. A 95% confidence interval (CI) is labeled at each point with the all-subject mean at the center. Average mean trending is indicated by the line connecting data points. IOP was measured for all subjects using Goldmann applanation (pre-/post-), iCARE (in-bed, 11 subjects), and Tonopen (in-bed, 5 subjects). Tonopen used for 5 subjects due to delays in procuring iCARE. RNFL thickness changes were determined via spectral-domain optical coherence tomography (OCT). No statistically significant changed was measured. A statistically significant decrease in central subfield thickness (macula) was determined using Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA; vers. 5.0).

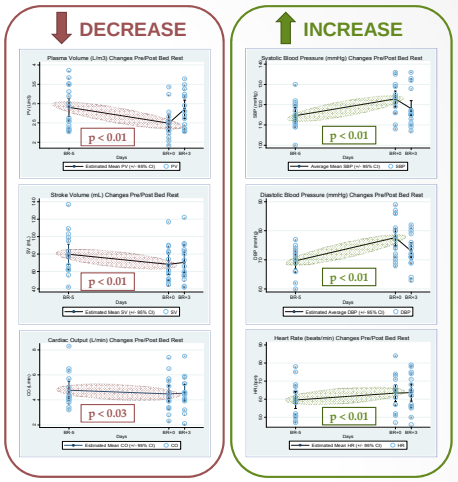
• No significant correlation was found between IOP and cardiovascular changes using a Somers's d non-parametric measure of association.

Variable (vs. IOP)	Coefficient	Standard Error	p
PV	-0.14	0.23	**0.54**
SV	0.11	0.23	**0.62**
HR	0.15	0.28	**0.58**
SBP	0.02	0.21	**0.93**
DBP	-0.26	0.23	**0.62**

Fig. 2. A Somers's d non-parametric measure of association was used to assess correlation between changes in intraocular pressure (IOP) and cardiovascular (CV) variables. No statistically significant p values were seen when comparing all of the CV variables (Plasma Volume/PV, Stroke Volume/SV, Heart Rate/HR, Systolic Blood Pressure/SBP, Diastolic Blood Pressure/DBP) to IOP.

RESULTS

• No data available relating fluid shifts to changes in IOP during in-bed rest due to experimental design of the study.



	Plasma Vol (L/m²)			Stroke Vol (mL)			Cardiac Output (L/min)		
Day	BR-5	BR+0	BR+3	BR-5	BR+0	BR+3	BR-5	BR+0	BR+3
Mean	2.90	2.49	2.86	79.73	68.13	70.40	4.78	4.48	4.54
CI +/- 95%	2.67/3.13	2.26/2.72	2.62/3.09	68.31/91.15	59.71/79.55	58.98/81.82	4.09/5.47	3.79/5.17	3.85/5.23
p (BR-5/BR+3)			0.66			<0.01			0.08
p (BR-5/BR+0)		<0.01			<0.01			0.03	
Measure	Heart Rate (bpm)			Systolic BP (mmHg)			Diastolic BP (mmHg)		
Day	BR-5	BR+0	BR+3	BR-5	BR+0	BR+3	BR-5	BR+0	BR+3
Mean	59.56	63.38	63.63	114.63	122.88	118.06	69.69	77.69	73.06
CI +/- 95%	54.84/64.29	58.65/68.10	58.90/68.35	110.69/118.56	118.94/126.80	114.13/121.99	66.86/72.51	74.86/80.51	70.23/75.89
p (BR-5/BR+3)			<0.01			0.07			<0.01
p (BR-5/BR+0)		<0.01			<0.01			<0.01	

Fig. 3. Summary of cardiovascular deconditioning. These measures were collected before and after bed rest (BR-5, BR+0, BR+3). Stroke volume, plasma volume, and cardiac output all documented decreases from pre-bed rest values. Heart rate and both systolic and diastolic blood pressure values increased over their baseline values. Mixed effects linear regression modeling was performed to determine the estimated means and confidence internals (CI) of each measure.

CONCLUSIONS

• Mean IOP significantly increased while at 6° HDT and returned towards pre-bed rest values upon leaving bed rest.
• While mean IOP increased during bed rest, it remained within the normal limits for subject safety.
• A diuretic shift and cardiovascular deconditioning occurs during in-bed rest, as expected.
• There was no demonstrable correlation between the largest change in IOP (pre/post) and cardiovascular measure changes (pre/post).
• Additional mixed effects linear regression modeling may reveal some subclinical physiological changes that might assist in describing the VIIP syndrome pathophysiology.

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DISCLOSURE

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